UNRELATED DONOR CORD BLOOD TRANSPLANTATION FOR CHILDREN WITH SEVERE SICKLE CELL DISEASE: RESULTS OF A PHASE II STUDY FROM THE BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK


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Most children with sickle cell disease (SCD) who might otherwise be considered for curative hematopoietic cell transplantation (HCT) lack a healthy matched related donor. Barriers to alternate donor HCT for SCD include graft rejection, graft-versus-host disease (GVHD) and regimen-related toxicities. To address these problems, we initiated a Phase II trial of unrelated cord blood or cord blood transplantation (CBT) using a novel, alemtuzumab-based, reduced intensity conditioning (RIC) regimen in children with severe SCD. Here we report the results for the 8 children who received CBT on this study. Patients were prepared for HCT following alemtuzumab (10, 15 and 20 mg on day -21, -20 and -19 respectively), fludarabine (30 mg/m2 day -8 to -4) and melphalan (140 mg/m2 day -3). Cyclosporine or tacrolimus and mycophenolate mofetil were administered for GVHD prophylaxis. Donor/recipient HLA match status was 5/6 in all patients based on low/intermediate resolution molecular typing at HLA -A, -B, and high resolution typing at -DRB1. Median recipient age was 13.7 years and median recipient HLA match status was 5/6 in all patients based on low/intermediate resolution molecular typing at HLA -A, -B, and high resolution typing at -DRB1. Median recipient age was 13.7 years and median recipient HLA match status was 5/6 in all patients based on low/intermediate resolution molecular typing at HLA -A, -B, and high resolution typing at -DRB1.

All patients are durably engrafted, with a median time to engraftment of 500 days (range 11-18) and platelets >20,000 of 13 days (range 30-36). Peripheral blood CD3+ and CD15+ cell chimerism from the 4 patients at the time of last follow-up are reported. Patient 1, day post-transplant (DPT) 329, (CD3+ 99%, CD15+ 98%), CD19+ (NiCord-92%, unmanipulated-86%), CD56+ (NiCord-76%, 50% unmanipulated). Patient 2, day +180; CD3 (NiCord–100%), CD19 (NiCord–100%), CD15 (NiCord–100%). Patient 3, day +60; CD3 (NiCord–91%, host-7%), CD15 (NiCord–98%, host-2%) Patient 4, day +60; CD3 (unmanipulated–100%), CD15 (unmanipulated–100%). There were no infection-related or unexpected adverse events and all patients are alive and well without GVHD. These data demonstrate prompt and prolonged engraftment of both myeloid and lymphoid cells derived from expanded HPCs (NiCord) in 3 of 4 patients treated to date. Longer follow-up is required to confirm durability.

SPACE AND TOLERANCE ARE CRITICAL FOR ENGRAFTMENT OF HEMATOPOIETIC ALLOGRAFTS IN RECIPIENTS CONDITIONED WITH TOTAL LYMPHOID IRRADIATION PLUS ATG

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Total lymphoid irradiation (TLI) is a unique non-myeloablative conditioning regimen for allogeneic hematopoietic cell transplantation (HCT) that targets major lymph node groups, but spares areas of normal marrow (BM). Such radiation plus anti-thymocyte globulin (ATG) create a tolerogenic host environment, permitting donor engraftment while ameliorating GVHD. Here we studied the role of tolerance induction, immune- and spatial barriers that hematopoietic stem cells (HSC) encounter in mice conditioned with TLI/ATG. TLIx3ATG were more lymphoablative than thalidomide total body irradiation (TBI). Lymphoablation was accompanied by a proportional (but not absolute) increase of T regulatory cell (Tregs) post-TLI/ATG. Long-term HSC (CKit+Sca+Lin-CD34-Fit3-Slam+) were normal in number in unexposed legs, increased in spleen and liver, but eradicated in irradiated spines. To segregate the effects of host barriers from facilitating donor cells or graft vs host reactivity, purified HSC (CKit+Thy1.1LoSca+Lin-) were used as grafts. Bioluminescence imaging revealed that across different genetic barriers, overall, donor cell expansion was slower in TLI/ATG vs TBI-treated hosts, and donor hematopoiesis was restricted to exposed spine areas. FACS analyses confirmed that 4 wks after TLI/ATG + congenic or minor antigen mismatched HCT hematopoiesis in the BM of shielded legs was fully host-derived, and only areas within the TLI field contained myeloid blood cells, including the HSC. The degree of donor chimerism differed between blood lineages, but remained stable over time. All T cell progenitor stages in the thymus had similar proportions of donor contribution, implying that the degree of donor chimerism is determined by the available space in the BM early post-TLI. The importance of tolerance-inducing host cells (Treg, NKt) was illustrated using TLI/ATG-conditioned Rag2−/− recipients (no NK, T, or B cells), which, despite their lack of classical cellular immune barriers,
had worse engraftment compared to congenic wildtype mice. In conclusion, both, vacating of HSC niche space, and the effects of host regulatory cells, that are activated during the TLI procedure appear critical to permit donor HSC engraftment post-TLI/ATG. The dynamics of engraftment after TLI/ATG are unique. Further studies to define the exact roles of host Tregs and NKT cells in engraftment after TLI/ATG and other conditioning modalities are underway.

330 IMMUNE RECONSTITUTION AND CLINICAL OUTCOME AFTER HSCT INFUSION FOR SEVERE COMBINED IMMUNODEFICIENCY IN NEWCASTLE Moreira, D.1, Slater, M.1, Nadenre, Z.2, Brigham, K.3, Barge, D.3, Jackson, A.3, Flood, T.1, Cant, A.1, Atkinson, M.5, Hambleton, S.2, Gennery, A.2 1 Newcastle upon Tyne Hospital NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; 2 Newcastle University, Newcastle upon Tyne, United Kingdom; 3 Newcastle upon Tyne Hospital NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; 4 Newcastle upon Tyne Hospital NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; 5 Newcastle upon Tyne Hospital NHS Foundation Trust, Newcastle upon Tyne, United Kingdom

Background: Hematopoietic stem cell transplantation (HSCT) is the treatment of choice for severe combined immunodeficiency (SCID). There remains debate on whether to pre-condition with chemotherapy prior to infusion of stem cells. We aimed to determine the long-term progress of classic SCID children who have undergone HSCT infusion at our centre, with respect to clinical outcome and immune recovery, and outcome based on transplant at <3 or >3 months of age, and molecular diagnosis.

Methods: A retrospective case note review of patients undergoing a first HSCT infusion for classic SCID from 01/1995 to 02/2011, surviving >2 months. Patients with previous HSCT were excluded. Parameters analyzed included clinical outcome, chimerism, lymphocyte subsets including recent thymic emigrants, specific antibody levels and Ig replacement. Statistical analysis was performed using c² (Fisher exact test) and nonparametric wilcoxon rank sum. A 2-sided p value <0.05 was considered significant.

Results: Twenty seven of 100 patients with SCID treated fulfilled the study criteria; 10 had ADA deficiency, 7 had T-B-NK+ phenotype, 8 had CqC/JAK3 SCID, and 2 had other forms of SCID. 12 were transplanted <3 months of age, median age at HSCT was 3 months (range 0-8 months). Twenty had infection at diagnosis, all >3 months. Eleven had MSD, 1 MMSD, 5 MFD, 3 MMFD, 6 MUD, 1 MMUD. Twenty received GVHD prophylaxis. Median follow-up was 80 months (2-187). Seven developed grade II-IV GVHD, 3 grade III. Five were re-transplanted, 2 received boost infusion for poor engraftment (1 CqC, 1 T-B-NK+), 3 received a conditioned HSCT (3 T-B-NK+). TRM was 11% (1 ADA, 2 T-B-NK+). Neurological and autoimmune complications were more common in the ADA and T-B-NK+ groups. Recent thymic emigrants were most commonly present in the CqC/JAK3 and ADA groups, and absent from the T-B-NK+ group. The ADA group had the most complete donor chimerism including myeloid chimerism, T-B-NK+ SCID only achieved donor T cell chimerism. Most ADA patients discontinued IVIG, compared to none with T-B-NK+ SCID.

Conclusion: HSCT infusion is an effective treatment for SCID. Best results are obtained if transplanted <3 months of age. Establishment of donor B cell chimerism may require additional therapies to achieve engraftment within the stem cell niche in all but ADA SCID.

331 DECITABINE IN COMBINATION WITH DONOR LYMPHOCYTE INFUSION AS SALVAGE THERAPY FOR RELAPSED AML POST-ALLOGENIC STEM CELL TRANSPLANTATION Kritharidis, A., Donahue, L.L., Keyzner, A., Devoe, C., Bayer, R.L. Hofstra University School of Medicine, North Shore LIJ Health System, Lake Success, NY

Prognosis is extremely poor for AML patients who relapse after allogeneic stem cell transplantation. Donor Lymphocyte infusions (DLI) can be used to salvage these patients with complete response rates reported to be 10-15% with an associated 40-60% chance of developing clinically significant GVHD. The mechanism by which DLI results in clinical responses is thought to be a T-cell mediated process. Data suggest that DLI normalizes the T-cell receptor repertoire and expands the anti-leukemic cell population. Hypomethylating agents, which appear to foster the graft versus leukemia phenomenon, were combined with DLI in attempt to enhance the graft versus leukemia effect. We report ten AML patients who received Decitabine +/- Etoposide with incremental DLI as salvage after relapse from allogeneic stem cell transplantation during the years 2007-2010. These patients were between the ages of 26-73 years. Six patients had de novo AML. Three patients were transformed from MDS, and one from essential thrombocytemia. Eight patients had reduced intensity conditioning regimens. Two patients received a fully ablative preparative regimen. Average time to progression post transplant was 17 months. Patients received Decitabine at 20mg/m² for 5-10 days, some in combination with Etoposide for 3-5 days for disease control. Patients received 1-4 courses of treatment approximately every 28 days with DLI between days 14-21. Two patients who progressed while receiving Decitabine/Etoposide received Clofarabine at 20-25mg/m² for 5 days, with subsequent DLI. Cell dose ranged from 1.27 to 31.7 CD3+ cells/kg. Two patients received a mobilized DLI. Six out of ten patients regained full chimerism. One patient who relapsed with extra medullary disease never lost his graft. Seven out of ten patients achieved a complete remission. Only one patient developed Grade 2 GVHD of the skin. Overall survival in these patients after relapse from allogeneic transplantation was 10.8 months.

The combination of Decitabine and DLI is a well tolerated outpatient therapeutic option for patients with relapsed AML post allogeneic stem cell transplantation. The majority of patients regained full chimerism and achieved complete remission with little or no GVHD.

332 IS THE USE OF 9/10 HLA UNRELATED DONORS STILL ACCEPTABLE IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR HEMATOLOGICAL MALIGNANCIES? COMPARISON WITH TRANSPLANTS FROM 10/10 HLA UNRELATED DONORS AND SIBLINGS Michallet, M., Sobh, M., Morisset, S., Detrait, M., Labussiere, H., Tedone, N., Ducastelle, S., Barraco, F., Chegboum, Y., Thomas, X., Nicolini, F.E. Centre Hospitalier Lyon Sud, Pierre Beteille, France

To evaluate the outcome of allo-HSCT from 9/10 HLA mismatched unrelated donors compared to those from 10/10 HLA identical unrelated donors and siblings; we retrospectively studied the outcome of 213 patients who received allo-HSCT for different hematological malignancies, 121 (57%) from HLA identical siblings, 63 (29%) from 10/10 HLA identical unrelated donors and 29 (14%) from 9/10 HLA mismatched unrelated donors between 2006 and 2011 at our institution. The different patient characteristics and figures will be provided in the future during the presentation. After HSCT, engraftment was significantly lower in the 9/10 HLA group (90%) than in the 10/10 HLA group (95%) than in the sibling group (99%); (p = 0.03); the cumulative incidence of acute GVHD> = 2 at 3 months was 42% (23-41), 20% (15-26) and 27% (23-32) respectively. The cumulative incidence of extensive chronic GVHD at one year was 21% (13-30), 9% (5-13) and 17% (14-21) for the 3 groups respectively. After a median follow-up of 8 months (0-54) in the 9/10 HLA group, 10 months (0-60) in the 10/10 HLA group and 18 months in the sibling group, the median OS was 10 months (5-21), 18 months (11-NR) and 60 months (31-NR) respectively with a 2-years probability of 19% (8-48), 43% (31-59) and 63% (54-74) respectively. There was a higher but not significant relapse incidence at one year in the 9/10 HLA group compared to other groups while the TRM was significantly higher with a cumulative incidence at 1 year of 45% (35-55) vs. 33% (27-39) for 10/12 and 12% (9-15) for siblings; (p<0.001). In multivariate analysis, OS was negatively affected by unrelated donors [HR = 5 (2.7-10), p = 0.0001]; 10/10 HR = 2 (1.2-4), p = 0.001; 9/10 HR = 2 (1.4-4), p = 0.003) and disease status < CR1 or <c>chronic phase 1 [HR = 5 (1.4-6), p = 0.003]; while the TRM was negatively affected by